1 SYNOPSIS

Study ID Eudract N°	Ro-CHOP Study 2012-001580-68
Title of the study	Phase 3 Multi-center Randomized Study to Compare Efficacy and Safety of Romidepsin CHOP (Ro-CHOP) versus CHOP in Subjects with Previously Untreated Peripheral T-Cell Lymphoma.
Protocol version	5.0
Investigational product	Romidepsin
Sponsor	LYSARC
Coordinating investigator Co-coordinating investigator	Pr Emmanuel Bachy Dr Vincent CAMUS
Centers	LYSA centers from France, Belgium and Portugal and centers from European, Asian countries and Australian area may enroll patients in this study.
Study Objectives	Primary objective of the study is to compare the efficacy of romidepsin when administered with CHOP versus CHOP alone in subjects with previously untreated peripheral T-cell lymphoma (PTCL) in terms of progression-free survival (PFS) using assessment of progressive disease according to malignant lymphoma criteria (1999) by Response Adjudication Committee (RAC). <u>Secondary objectives</u> are to compare Ro-CHOP between CHOP alone in term of: • Overall survival • Overall Response Rate (ORR [PR+CR+CRu]) (according to the Response criteria for malignant lymphoma 1999) • Duration of response • Time to progression • Time to treatment failure • Safety • Quality of Life (QoL) • Response rates by PTCL histological subtypes • Response rate by standard prognostic parameters <u>Exploratory objectives</u> are: • Evaluation of tumor response rate by FDG-PET scan assessment (Revised response criteria for malignant lymphoma 2007) • Analysis of the concordance between investigator-assessed and centrally reviewed efficacy data • Impact of circulating tumoral cell load and circulating EBV load at

	diagnosis, on the treatment response • Define the molecular signature(s) (gene expression and mutations) of various PTCL entities and correlate these signatures with response to therapy, especially romidepsin efficacy • Determine novel molecular predictive factors of response to Romidepsin-CHOP treatment • Determine feasibility and clinical impact of cell free DNA sequencing in PTCL
Duration of the study	Patients will receive study drug for up to 6 cycles, or until unacceptable toxicity develops or until disease progression or voluntary withdrawal. Patients will be followed until five years after the last randomized patient.
Number of patients.	Approximately 420 subjects will be enrolled in the study.
Inclusion and exclusion criteria	**Inclusion criteria** Patients must satisfy all following criteria to be enrolled in the study: 1. Males and females of 18 years of age to 80 years of age. 2. Understand and voluntarily sign an informed consent document prior to any study related assessments/procedures are conducted. 3. Able to adhere to the study visit schedule and other protocol requirements. 4. Patients with histologically proven peripheral T-cell lymphoma (PTCL), not previously treated; the following subtypes as defined by the WHO classification (2008;2011) may be included, whatever the Ann Arbor stage (I - IV): a. Nodal types: i. PTCL, not otherwise specified ii. Angioimmunoblastic T-cell lymphoma iii. Anaplastic large cell lymphoma, ALK-negative type b. Extra-nodal types: i. Enteropathy-associated T-cell lymphoma ii. Hepato-splenic T-cell lymphoma iii. Subcutaneous panniculitis-like T-cell lymphoma iv. Primary cutaneous gamma-delta T-cell lymphoma v. Primary cutaneous CD8+ aggressive epidermotropic lymphoma vi. Primary cutaneous CD4+ small/medium T-cell lymphoma c. Other non classifiable peripheral T-cell lymphoma 5. ECOG performance status 0, 1 or 2 6. Negative pregnancy test for females of childbearing potential (FCBP) 7. Female patients of child bearing potential must use an effective method of birth control (i.e. hormonal contraceptive, intrauterine device, diaphragm with spermicide, condom with spermicide or abstinence) during treatment period and 1 month thereafter; Males must use an effective method of birth control during treatment period and 3 months

thereafter.

8. Life expectancy of ≥ 90 days (3 months).

Exclusion criteria

Presence of any of the following will exclude a patient from enrollment:

1. Any significant medical condition, laboratory abnormality, or psychiatric illness that would prevent the patient from participating in the study.
2. Any condition that confounds the ability to interpret data from the study.
3. Other types of lymphomas, e.g. B-cell lymphoma
4. The following types of T cell lymphomas:
   a. Adult T-cell lymphoma/leukemia (HTLV-1 related T-cell lymphoma)
   b. Extranodal T-cell/NK-cell lymphoma, nasal type
   c. Anaplastic large cell lymphoma, ALK-positive type
   d. Cutaneous T cell lymphoma (mycosis fungoides, Sézary syndrome)
   e. Primary cutaneous CD30+ T-cell lymphoproliferative disorder
   f. Primary cutaneous anaplastic T-cell lymphoma
5. Previous treatment for PTCL with immunotherapy or chemotherapy except for short-term corticosteroids (duration of ≤ 8 days) before randomization
6. Previous radiotherapy for PTCL except if localized to one lymph node area
7. Patients planned for autologous or allogeneic transplant as consolidation in first line
8. Central nervous system -meningeal involvement
9. Contraindication to any drug contained in the chemotherapy regimen,
10. Subjects with HIV positivity
11. Subjects with active hepatitis B or C. Chronic carriers of hepatitis B without HBV DNA positive blood are eligible after advice from hepatologist and initiation of prophylactic treatment if needed. Subjects with non-active hepatitis C (with normal transaminases) are eligible. Patients with HBc Ab+/ HBs Ab+/ HBs Ag- and HBV DNA- should be referred to an hepatologist and a prophylactic treatment should be initiated if needed
12. Any of the following laboratory abnormalities, except if secondary to the lymphoma:
    a. Absolute neutrophil count (ANC) < 1,500 cells/mm^3 (1.5 x 10^9/L),
    b. Platelet count < 100,000/mm^3 (100 x 10^9/L), or < 75,000/mm^3 if bone marrow is involved,
    c. Serum SGOT/AST or SGPT/ALT ≥ 3.0 x upper limit of normal (ULN),
    d. Serum total bilirubin > 2 x ULN, except in case of hemolytic anemia,
    e. K^+ and Mg^{2+} levels < LLN, except if corrected per protocol guidance

	before beginning the romidepsin infusion 13. Serum creatinine > 2.0 x ULN 14. Prior history of malignancies other than lymphoma (except for basal cell or squamous cell carcinoma of the skin or carcinoma in situ of the cervix or breast or untreated prostatic cancer without any plan for a treatment) unless the patient has been free of the disease for ≥ 3 years 15. Any serious medical condition, laboratory abnormality, or psychiatric illness that would prevent the patient from signing the informed consent form 16. Any known cardiac abnormalities such as: a. Patients with congenital long QT syndrome b. Corrected QT interval > 480 msec (using the Fridericia formula) c. Myocardial infarction within 6 months of cycle 1 day 1 d. History of or concomitant significant cardiovascular disease e. Ejection fraction <45% by MUGA scan or by echocardiogram; 17. Concomitant use of drugs that may cause a significant prolongation of the QTc 18. Patients who have received more than 200 mg/m^2 doxorubicin 19. Concomitant use of strong CYP3A4 inhibitors 20. Concomitant use of therapeutic warfarin due to a potential drug interaction. Use of a low dose of warfarin or another anticoagulant to maintain patency of venous access port and cannulas is permitted. 21. Clinically significant active infection 22. Use of any standard or experimental anti-cancer drug therapy within 28 days of the initiation (Day 1) of study drug 23. Pregnant or lactating females or women of childbearing potential not willing to use an adequate method of birth control for the duration of the study. For German patients only: 24. Patients institutionalized by official means or court order
Design of the trial	This study is an open label, multicenter study. Subjects are randomized at a 1:1 ratio to receive either (arm A) cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) or (arm B) romidepsin administered IV at day 1 and day 8 in combination with CHOP administered every 3 weeks for 6 cycles in patients with previously untreated peripheral T-cell lymphoma.
Study Treatment	**Study Treatments** All patients will be treated with either CHOP or Ro-CHOP in three-week cycles for 6 cycles.

Drug	Dose	Schedule
Cyclophosphamide	750mg/m² IV	Day 1
Doxorubicin	50 mg/m² IV	Day 1
Vincristine	1.4 mg/m² (max 2 mg) IV	Day 1
Prednisone	40 mg/m² PO	Days 1-5

	Romidepsin (Ro-CHOP arm only) | 12mg/m² IV | Days 1 and 8 **Overview of Efficacy Assessments** Tumor assessment (clinical examination, laboratory tests, pelvis, abdominal, chest and cervical CT scan, bone marrow examination) will be performed at baseline, after 3 cycles of treatment (only a CT scan performed), and 4 weeks after the last treatment dose. To ensure comparability, baseline and on-study methods for response assessment will be performed using identical techniques. Follow-up assessment, including CT Scan, will be clinical visit every 3 months the first year, then every 4 months the 2nd year, and every 6 months thereafter. **Overview of Safety Assessments** Clinical examination (including vital signs, ECOG performance status) and laboratory tests (including complete blood counts, serum chemistries) will be obtained prior to drug administration, before each cycle of treatment and at 4 weeks after the last study treatment administration. Electrocardiogram will be performed just before romidepsin infusion **(**after administration of antiemetic premedication if possible) at day 1 of each cycle for measurement of corrected QT interval according to the Fridericia formula and in case of cardiac event or clinical signs compatible with heart rhythm disorder and in case of biological abnormalities. In addition, complete blood cell counts will be obtained at day 8, day 10 and day 14 for all patients. AEs/SAEs type, severity (according to NCI-CTCAE v. 4.03), cycle, duration, seriousness and relationship to study treatment will be assessed throughout the study. Laboratory abnormalities will be assessed according to the NCI-CTCAE v. 4.03.
Registration in the study/ Randomization	Once a patient signs written consent, the subject may enter the screening period, which is permitted to last up to 4 weeks. During the screening period, the patient will undergo safety and other assessments to determine eligibility for the study and undergo randomization to either experimental arm (romidepsin plus CHOP) versus control arm (CHOP alone). Screening and randomization will be performed via IWRS. The stratification will be performed with the following factors: - the IPI score at baseline (<2 vs. ≥2), - age (≤60 vs >60), and investigator-assessed histology type (nodal vs. extranodal histology)
Statistical analysis	**SAMPLE SIZE CALCULATION** Assumptions: alpha =2.5% (1-sided test), power =80%, Drop-out at 12 months=10%, Accrual rate: a linear ramp up of accrual during the first 6 months until it reaches a constant accrual rate of 10.5 patient/month afterwards, HR = 0.7143 (median PFS in the control arm = 12 mos vs 16.8 mos), Accrual period=~43mos, Study duration=~60mos, One interim analysis for futility, N=420 (210 in each arm) for 278 events.

	All sample size calculations are based on East, version 5. **ANALYSIS PLAN** Primary analysis between the two study arms will be one-sided stratified log-rank test at 2.5% significance level. Stratification factors will be those used for randomization (see section below on Registration in the study/ Randomization). Estimates of treatment effect will be expressed as hazard ratios including two-sided 95% confidence intervals. In addition, Kaplan-Meier estimates of median progression-free survival as well as progression-free survival rates at one, two and three years after randomization with 95% confidence intervals will also be reported. Overall Survival will be defined as a key secondary efficacy endpoint. Secondary time to event endpoints will be analyzed by using a two-sided stratified log-rank test. Overall response rate at the end of the treatment phase will be compared according to treatment arm using Cochran-Mantel-Haenszel Test. **INTERIM ANALYSIS** One interim analysis for futility will be performed during the conduct of the study. The statistical evaluation will be done on the primary endpoint criterion. Futility boundary is based on G (-4) beta spending function. Study will be recommended to terminate if the observed HR (Ro-CHOP versus CHOP) is greater than 1.2027 (corresponding to z-score <-0.8431). Futility boundary is non-binding and there is no alpha buy-back which is being taken into account in sample size/power considerations. The approximate timing of the interim analysis is after 30% (84 events) of total number of planned events (278 events) which is projected to occur at about the 25th month from study start. **PRIMARY ANALYSIS** The primary PFS analysis will be performed when 278 centrally adjudicated progression/death events have been reached or 2 years after the last patient is randomized in the study, whichever occurs first. Overall survival will be analyzed at the time of PFS analysis and will be updated at the study closure. As a key secondary endpoint and in order to ensure an overall two-sided 0.05 study-wise Type I error rate, a fixed-sequence gate-keeping procedure will be used to interpret the analysis results of the OS. Therefore, OS analysis will be performed only if PFS analysis is significant ($p \leq 0.05$). In that case, OS efficacy claims will be made if OS analysis p-value ≤ 0.05
Planned start/end of recruitment	January 2013 – January 2018